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THE MEMBRANE EQUATION

Any physical or biophysical mechanism instantiating an information processing system that needs to survive in the real world must obey several constraints: (1) it must operate at high speeds, (2) it must have a rich repertoire of computational primitives, with the ability to implement a variety of linear and nonlinear, high-gain, operations, and (3) it must interface with the physical world—in the sense of being able to represent sensory input patterns accurately and translate the result of the computations into action, that is motor output (Keyes, 1985).

The membrane potential is the one physical variable within the nervous system that fulfills these three requirements: it can vary rapidly over large distances (e.g., an action potential changes the potential by 100 mV within 1 msec, propagating up to 1 cm or more down an axon within that time), and the membrane potential controls a vast number of nonlinear gates—ionic channels—that provide a very rich substrate for implementing nonlinear operations. These channels transduce visual, tactile, auditory, and olfactory stimuli into changes of the membrane potential, and such voltage changes back into the release of neurotransmitters or the contraction of muscles.

This is not to deny that ionic fluxes, or chemical interactions of various substances with each other, are not crucial to the working of the brain. They are, and we will study some of these mechanisms in Chap. 11. Yet the membrane potential is the incisive variable that serves as primary vehicle for the neuronal operations underlying rapid computations—at the fraction of a second time scale—in the brain.

We will introduce the reader in a very gentle manner to the electrical properties of nerve cells by starting off with the very simplest of all neuronal models, consisting of nothing more than a resistance and a capacitance (a so-called *RC circuit*). Yet endowed with synaptic input, this model can already implement a critical nonlinear operation, *divisive normalization* and *gain control*.

1.1 Structure of the Passive Neuronal Membrane

As a starting point, we choose a so-called *point* representation of a neuron. Here, the spatial dependency of the neuron is reduced to a single point or compartment. Such an

approximation would be valid, for instance, if we were investigating a small, spherical cell without a significant dendritic tree.

1.1.1 Resting Potential

The first thing we notice once we managed to penetrate into this cell with a wire from which we can record (termed an intracellular *microelectrode*) is the existence of an electrical potential across this membrane. Such experiments, carried out in the late 1930s by Cole and Curtis (1936) in Woods Hole, Massachusetts, and by Hodgkin and Huxley (1939) on the other side of the Atlantic, demonstrated that almost always, the membrane potential, defined as the difference between the intracellular and the extracellular potentials, or

$$V_m(t) = V_i(t) - V_e(t), \tag{1.1}$$

is negative. Here t stands for time. In particular, at rest, all cells, whether neurons, glia or muscle cells, have a negative resting potential, symbolized throughout the book as V_{rest}. Depending on the circumstances, it can be as high as -30 mV or as low as -90 mV. Note that when we say the cell is at "rest," it is actually in a state of dynamic equilibrium. Ionic currents are flowing across the membrane, but they balance each other, in such a manner that the net current flowing across the membrane is zero. Maintaining this equilibrium is a major power expenditure for the nervous system. Half of the metabolic energy consumed by a mammalian brain has been estimated to be due to the membrane-bound pumps that are responsible for the upkeep of the underlying ionic gradients (Ames, 1997).

The origin of V_{rest} lies in the differential distribution of ions across the membrane, which we do not further describe here (see Sec. 4.4 and Hille, 1992). V_{rest} need not necessarily be fixed. Indeed, we will discuss in Sec. 18.3 conditions under which a network of cortical cells can dynamically adjust their resting potentials.

1.1.2 Membrane Capacity

What is the nature of the membrane separating the intracellular cytoplasm from the extracellular milieu (Fig. 1.1)? The two basic constitutive elements of biological membranes, whether from the nervous system or from nonneuronal tissues such as muscle or red blood cells, whether prokaryotic or eukaryotic, are *proteins* and *lipids* (Gennis, 1989).

The backbone of the membrane is made of two layers of phospholipid molecules, with their polar heads facing the intracellular cytoplasm and the extracellular space, thereby separating the internal and external conducting solutions by a 30–50-Å-thin insulating layer. We know that whenever a thin insulator is keeping charges apart, it will act like a *capacitance*. The capacitance C is a measure of how much charge Q needs to be distributed across the membrane in order for a certain potential V_m to build up. Or, conversely, the membrane potential V_m allows the capacitance to build up a charge Q on both sides of the membrane, with

$$Q = CV_m. \tag{1.2}$$

In membrane biophysics, the capacitance is usually specified in terms of the *specific membrane capacitance* C_m, in units of microfarads per square centimeter of membrane area (μF/cm^2). The actual value of C can be obtained by multiplying C_m by the total membrane area. The thickness and the dielectric constant of the bilipid layer determine the numerical value of C_m. For the simplest type of capacitance formed by two parallel plates, C_m scales

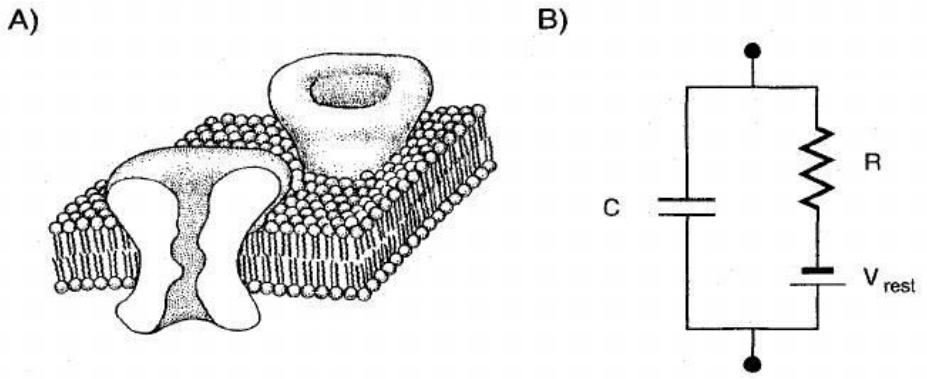

Fig. 1.1 Nature of the Passive Neuronal Membrane **(A)** Schematic representation of a small patch of membrane of the types enclosing all cells. The 30–50 Å thin bilayer of lipids isolates the extracellular side from the intracellular one. From an electrical point of view, the resultant separation of charge across the membrane acts akin to a capacitance. Proteins inserted into the membrane, here ionic channels, provide a conduit through the membrane. Reprinted by permission from Hille (1992). **(B)** Associated lumped electrical circuit for this patch, consisting of a capacitance and a resistance in series with a battery. The resistance mimics the behavior of voltage-independent ionic channels inserted throughout the membrane and the battery accounts for the cell's resting potential V_{rest}.

inversely with the thickness separating the charges (the thinner the distance between the two plates, the stronger the mutual attraction of the charges across the insulating material). As discussed in Appendix A, the specific capacitance per unit area of biological membranes is between 0.7 and 1 μF/cm^2. For the sake of convenience, we adopt the latter, simple to remember, value. This implies that a spherical cell of 5-μm radius with a resting potential of -70 mV stores about -0.22×10^{-12} coulomb of charge just below the membrane and an equal but opposite amount of charge outside.

When the voltage across the capacitance changes, a current will flow. This *capacitive current*, which moves on or off the capacitance, is obtained by differentiating Eq. 1.2 with respect to time (remember that current is the amount of charge flowing per time),

$$I_C = C\frac{dV_m(t)}{dt}. \tag{1.3}$$

For a fixed current, the existence of the membrane capacitance imposes a constraint on how rapidly V_m can change in response to this current; the larger the capacitance, the slower the resultant voltage change.

It is important to realize that there is never any actual movement of charge across the insulating membrane. When the voltage changes with time, the charge changes and a current will flow, in accordance with Eq. 1.3, but never directly across the capacitance. The charge merely redistributes itself across the two sides by way of the rest of the circuit.

Can any current flow directly across the bilipid layers? As detailed in Appendix A, the extremely high resistivity of the lipids prevents passages of any significant amount of charge across the membrane. Indeed, the specific resistivity of the membrane is approximately one billion times higher than that of the intracellular cytoplasm. Thus, from an electrical point of view, the properties of the membrane can be satisfactorily described by a sole element: a capacitance.

1.1.3 Membrane Resistance

With no other components around, life would indeed be dull. What endows a large collection of squishy cells with the ability to move and to think are the all-important *proteins* embedded within the membrane. Indeed, they frequently penetrate the membrane, allowing ions to pass from one side to the other (Fig. 1.1). Protein molecules, making up anywhere from 20 to 80% (dry weight) of the membrane, subserve an enormous range of specific cellular functions, including ionic channels, enzymes, pumps, and receptors. They act as doors or gates in the lipid barrier through which particular information or substances can be transferred from one side to the other. As we shall see later on, a great variety of such "gates" exists, with different keys to open them. For now, we are interested in those membrane proteins that act as ionic *channels* or *pores*, enabling ions to travel from one side of the membrane to the other. We will discuss the molecular nature of these channels in more detail in Chap. 8.

For now, we will summarily describe the current flow through these channels by a simple linear resistance R. Since we also have to account for the resting potential of the cell, the simplest electrical description of a small piece of membrane includes three elements, C, R, and V_{rest} (Fig. 1.1). Such a circuit describes a *passive* membrane in contrast to *quasi-active* and *active* membranes, which contain, respectively, linear, inductance-like, and nonlinear voltage-dependent membrane components. For obvious reasons, it is also sometimes known as an *RC circuit*. Fortuitously, the membranes of quite a few cells can be mimicked by such *RC* circuits, at least under some limited conditions.

The membrane resistance is usually specified in terms of the *specific membrane resistance* R_m, expressed in terms of resistance times unit area (in units of $\Omega \cdot \mathrm{cm}^2$). R is obtained by dividing R_m by the area of the membrane being considered. The inverse of R_m is known as the passive conductance per unit area of dendritic membrane or, for short, as the *specific leak conductance* $G_m = 1/R_m$ and is measured in units of siemens per square centimeter ($\mathrm{S/cm}^2$).

1.2 A Simple *RC* Circuit

Let us now carry out a virtual electrophysiological experiment. Assume that we have identified a small spherical neuron of diameter d and have managed to insert a small electrode into the cell without breaking it up. Under the conditions of our experiments, we have reasons to believe that its membrane acts passively. We would like to know what happens if we inject current $I_{inj}(t)$ through the microelectrode directly into the cell. This electrode can be thought of as an ideal *current source* (in contrast to an ideal voltage source, such as a battery).

How can we describe the dynamics of the membrane potential $V_m(t)$ in response to this current? The cell membrane can be conceptualized as being made up from many small *RC* circuits (Fig. 1.2A). Because the dimensions of the cell are so small, the electrical potential across the membrane is everywhere the same and we can neglect any spatial dependencies; physiologists will say the cell is *isopotential*. This implies that the electrical behavior of the cell can be adequately described by a single *RC* compartment with a current source (Fig. 1.2B). The net resistance R is determined by the specific membrane resistance R_m divided by the total membrane area πd^2 (since the current can flow out through any one part of the membrane) while the total capacitance C is given by C_m times the membrane area.

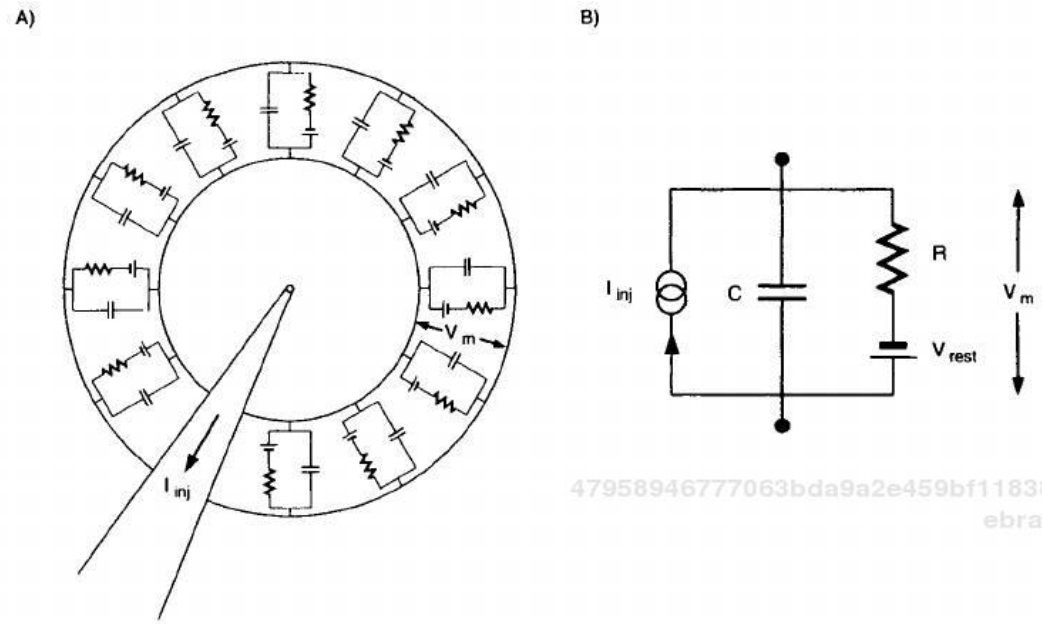

Fig. 1.2 Electrical Structure of a Small Passive Neuron **(A)** Equivalent electrical model of a spherical cell with passive membrane. An intracellular electrode delivers current to the cell. By convention, an outward current is positive; thus, the arrow. We assume that the dimensions of the cell are small enough so that spatial variations in the membrane potential can be neglected. **(B)** Under these conditions, the cell can be reduced to a single *RC* compartment in series with an ideal current source I_{inj}.

It is straightforward to describe the dynamics of this circuit by applying *Kirchhoff's current law*, which states that the sum of all currents flowing into or out of any electrical node must be zero (the current cannot disappear, it has to go somewhere). The current across the capacitance is given by expression 1.3. The current through the resistance is given by *Ohm's law*,

$$I_{\text{R}} = \frac{V_m - V_{\text{rest}}}{R} . \tag{1.4}$$

Note that the potential across the resistance is not equal to V_m, but to the difference between the membrane potential and the fictive battery V_{rest}, which accounts for the resting potential. Due to conservation of current, the capacitive and resistive currents must be equal to the external one, or

$$C\frac{dV_m(t)}{dt} + \frac{V_m(t) - V_{\text{rest}}}{R} = I_{\text{inj}}(t) . \tag{1.5}$$

With $\tau = RC$, with units of $\Omega \cdot \text{F} = \text{sec}$, we can rewrite this as

$$\tau\frac{dV_m(t)}{dt} = -V_m(t) + V_{\text{rest}} + RI_{\text{inj}}(t) . \tag{1.6}$$

A minor, but important detail is the sign of the external current (after all, we could have replaced $+I_{inj}$ by $-I_{\text{inj}}$ in Eq. 1.6). By convention, an outward current, that is positive charge flowing from inside the neuron to the outside, is represented as a positive current. An outward going current that is delivered through an intracellular electrode will make the inside of the cell more positive; the physiologist says that the cell is *depolarized*. Conversely,

an inward directed current supplied by the same electrode, plotted by convention in the negative direction, will make the inside more negative, that is, it will *hyperpolarize* the cell. If the current is not applied from an external source but is generated by a membrane conductance, the situation is different (see Chap. 5).

Due to the existence of the battery V_{rest}, the electrical diagram in Fig. 1.2B does *not*, formally speaking, constitute a *passive* circuit, since its current-voltage (I–V) relationship is not restricted to the first and third quadrants of the I–V plane. This implies that power is needed to maintain this I–V relationship, ultimately supplied by the differential distributions of ions across the membrane. Because the I–V relationship has a nonzero, positive derivative for every value of V_m, it is known as an *incrementally passive* device. This point is not without interest, since it relates to the stability of circuits built using such components (Wyatt, 1992). We here do not take a purist point of view, and we will continue to refer to a membrane whose equivalent circuit diagram is similar to that of Figs. 1.1B and 1.2B as passive.

Equation 1.6 is known as the *membrane equation* and constitutes a first-order, ordinary differential equation. With the proper initial conditions, it specifies an unique voltage trajectory. Let us assume that the membrane potential starts off at $V_m(t = 0) = V_{rest}$. We can replace this into Eq. 1.6 and see that in the absence of any input ($I_{inj} = 0$) this assumption yields $dV_m/dt = 0$, that is, once at V_{rest}, the system will remain at V_{rest} in the absence of any input. This makes perfect sense. So now let us switch on, at $t = 0$, a step of current of constant amplitude I_0. We should remember from the theory of ordinary differential equations that the most general form of the solution of Eq. 1.6 can be expressed as

$$V_m(t) = v_0 e^{-t/\tau} + v_1 \tag{1.7}$$

where v_0 and v_1 depend on the initial conditions. Replacing this into Eq. 1.6 and canceling identical variables on both sides leaves us with

$$v_1 = V_{rest} + RI_0 . \tag{1.8}$$

We obtain the value of v_0 by imposing the initial condition $V_m(t = 0) = v_0 + v_1 = V_{rest}$. Defining the steady-state potential in response to the current as $V_\infty = RI_0$, we have solved for the dynamics of V_m for this cell,

$$V_m(t) = V_\infty(1 - e^{-t/\tau}) + V_{rest} . \tag{1.9}$$

This equation tells us that the time course of the deviation of the membrane potential from its resting state, that is, $V_m(t) - V_{rest}$, is an exponential function in time, with a time constant equal to τ. Even though the current changed instantaneously from zero to I_0, the membrane potential cannot follow but plays catch up. This is demonstrated graphically in Fig. 1.3. How slowly V_m changes is determined by the product of the membrane resistance and the capacitance; the larger the capacitance, the larger the current that goes toward charging up C. Note that τ is independent of the size of the cell,

$$\tau = RC = R_m C_m . \tag{1.10}$$

As we will discuss in considerable detail in later chapters, passive time constants range from 1 to 2 msec in neurons that are specialized in processing high-fidelity temporal information to 100 msec or longer for cortical neurons recorded under slice conditions. A

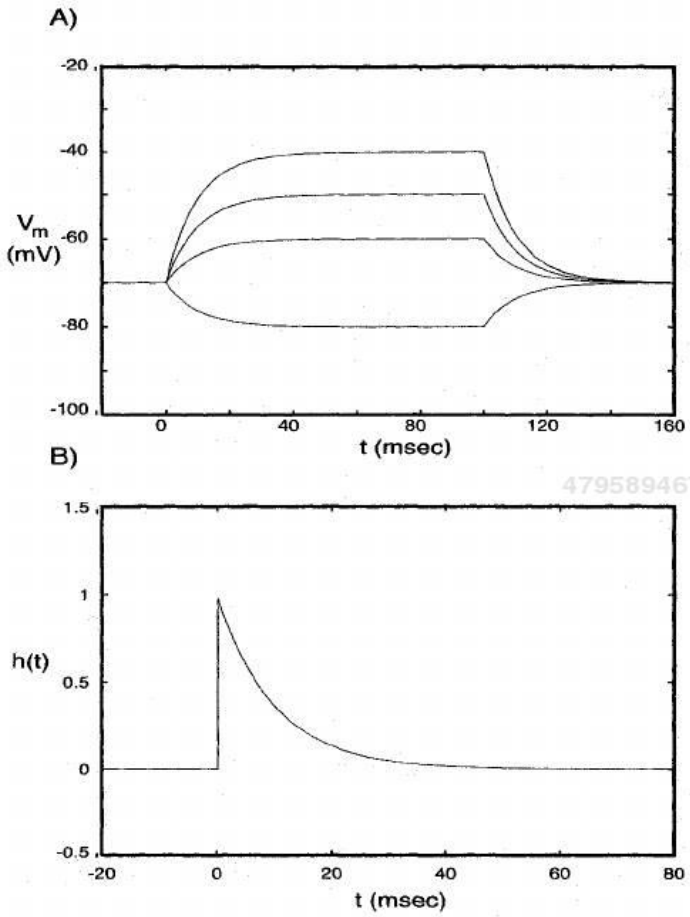

Fig. 1.3 BEHAVIOR OF AN *RC* CIRCUIT **(A)** Evolution of the membrane potential $V_m(t)$ in the single *RC* compartment of Fig. 1.2B when a current step of different amplitudes I_0 (see Eq. 1.9) is switched on at $t = 0$ and turned off at 100 msec. Initially, the membrane potential is at $V_{rest} = -70$ mV. We here assume $R = 100$ MΩ, $C = 100$ pF, $\tau = 10$ msec, and four different current amplitudes, $I_0 = -0.1, 0.1, 0.2$, and 0.3 nA. **(B)** Normalized *impulse response* or *Green's function* (Eq. 1.17) associated with the *RC* circuit of Fig. 1.2B. The voltage $V_m(t)$ in response to any current input $I_{inj}(t)$ can be obtained by convolving this function with the input.

typical range for τ recorded from cortical pyramidal cells in the living animal[1] is between 10 and 20 msec.

Remember the origin of the membrane capacitance in the molecular dimensions of the bilipid membrane. A thicker membrane would lead to a smaller value for C_m and faster temporal responses.[2]

The final voltage level in response to the current step is $RI_0 + V_{rest}$ (from Ohm's law). If $I_0 > 0$, the cell will depolarize (that is, $V_\infty > V_{rest}$), whereas for $I_0 < 0$, the converse occurs. The resistance R is also termed the *input resistance* of the cell; the larger R, the larger the voltage change in response to a fixed current. The input resistance at the cell bodies of neurons, obtained by dividing the steady-state voltage change by the current causing it, ranges from a few megaohms for the very large motoneurons in the spinal cord to hundreds of megaohms for cortical spiny stellate cells or cerebellar granule cells.

1. This is called *in vivo*. Such experiments need to be distinguished from the cases in which a very thin slice is taken from an animal's brain, placed in a dish, and perfused with a nutrient solution. This would be termed an *in vitro* experiment.

2. As an aside to the neuromorphic engineers among us designing analog integrated electronic circuits, $C_m = 1\ \mu F/cm^2$ is about 20 times higher than the specific capacitance obtained by sandwiching a thin layer of silicon dioxide between two layers of poly silicon using a standard 2.0 or 1.2 μm CMOS process (Mead, 1989).

What happens if, after the membrane potential reaches its steady-state value V_∞, the current is switched off at time t_{off}? An analysis similar to the above shows that the membrane potential returns to V_{rest} with an exponential time course; that is,

$$V_m(t) = V_\infty e^{-(t-t_{\text{off}})/\tau} + V_{\text{rest}} \tag{1.11}$$

for $t \geq t_{\text{off}}$. (This can be confirmed by placing this solution into Eq. 1.6; see also Fig. 1.3A.)

Now that we know the evolution of the membrane potential for a current step, we would like to know the solution in the general case of some time-dependent current input $I_{\text{inj}}(t)$. Are we condemned to solve Eq. 1.6 explicitly for every new function $I_{\text{inj}}(t)$ that we use? Fortunately not; because the *RC* circuit we have been treating here is a shift-invariant, linear system, we can do much better.

1.3 *RC* Circuits as Linear Systems

Linearity is an important property of certain systems that allows us—in combination with shift invariance—to completely characterize their behavior to *any* input in terms of the system's *impulse response* or *Green's function* (named after a British mathematician living at the beginning of the nineteenth century). Since the issue of linear and nonlinear systems runs like a thread through this monograph, we urge the reader who has forgotten these concepts to quickly skim through Appendix B, which summarizes the most relevant points.

1.3.1 Filtering by RC Circuits

Let us compute the voltage response of the *RC* circuit of Fig. 1.2B in response to a current impulse $\delta(t)$. We will simplify matters by only considering the deviation of the membrane potential from its resting state V_{rest}. Here and throughout the book we use $V(t) = V_m(t) - V_{\text{rest}}$ when we are dealing with the potential relative to rest and reserve $V_m(t)$ for the absolute potential. This transforms Eq. 1.6 into

$$\tau \frac{dV(t)}{dt} = -V(t) + R\delta(t)\,. \tag{1.12}$$

We can transform this equation into Fourier space, where $\tilde{V}(f)$ corresponds to the Fourier transform of the membrane potential (for a definition, see Appendix B). Remembering that the $dV(t)/dt$ term metamorphoses into $i2\pi\tilde{V}(f)\hat{V}(P)$, where $i^2 = -1$, we have

$$\tilde{V}(f) = \frac{R}{1 + i2\pi f\tau}\,. \tag{1.13}$$

A simple way to conceptualize this is to think of the input as a sinusoidal current of frequency f; $I_{\text{inj}}(t) = \sin(2\pi ft)$. Since the system is linear, it responds by a sinusoidal change of potential at the same frequency f, but of different amplitude and shifted in time: $V(t) = \tilde{A}(f)\sin(2\pi ft + \tilde{\phi}(f))$. The amplitude of the voltage response at this frequency, termed $\tilde{A}(f)$, is given by

$$|\tilde{A}(f)| = \frac{R}{\sqrt{1 + (2\pi f\tau)^2}} \tag{1.14}$$

and its phase by